Pediatric Advisory Subcommittee
Chronic Hepatitis C Backgrounder

I. HEPATITIS C IN ADULTS

A. Epidemiology and Natural History

Between 100,000 and 200,000 new infections with hepatitis C virus occur in the US each year. Of these only 20% are diagnosed in the acute stage, with approximately 80% developing chronic infection. It is estimated that nearly 3.0 million adults in the US are HCV carriers (~2% of the population). The primary mode of transmission in adults is parenteral, either through blood transfusions or sharing of needles by IV drug users. The risk of infusion-related hepatitis is approximately 1 in 100,000 units transfused.

Most adults acutely infected with HCV are asymptomatic and anicteric. Some patients (25 to 35%) develop fatigue, malaise, weakness, nausea, anorexia or become icteric. Most patients develop signs of liver cell injury within 50 days of exposure, as evidenced by elevation of serum alanine transferase (ALT). ALT levels can fluctuate widely, and the relationship between ALT and disease severity as judged by histology is inconsistent. HCV-RNA can usually be detected in the serum within 1-3 weeks. Antibodies to HCV become detectable early in the disease and are present in virtually all patients with chronic HCV infection; anti-HCV is detectable in 50-70% at the onset of symptoms and in 90% three months after onset of infection.

HCV infection is self-limited in only about 20% of cases as characterized by the disappearance of HCV-RNA and return of liver enzymes to normal. Approximately 80% of patients fail to clear the virus by 6 months and develop chronic hepatitis with persistent viremia. Although the rate of disease progression is variable, liver damage from chronic HCV infection generally progresses at a slow rate without signs or symptoms in the majority of patients during the first two decades after infection. Fulminant liver failure is a relatively rare late manifestation of chronic disease.

Approximately 20% of all chronically infected patients develop cirrhosis. A minority (approximately 20%) of patients with cirrhosis ultimately develop liver failure, portal hypertension and the associated conditions of ascites, esophageal varices and encephalopathy. Chronic HCV infection is also associated with increased risk of hepatocellular carcinoma (HCC). Risk factors associated with the development of HCV-related HCC include cirrhosis, male gender and older age.

B. Treatment of Chronic HCV in Adults
B.1. Measurements of treatment effect

The goal of therapy is to reduce the development of cirrhosis and HCC. However, because of the long delay until the occurrence of HCV-related end-stage liver disease or HCC, treatments to-date for HCV infection have been evaluated using surrogate endpoints that are measured in the short-term. Normalization of ALT levels and

improvements in liver histology using a standardized assessment have historically been used, for example, to demonstrate the efficacy of treatments for chronic HCV infection. Accumulating evidence suggests, however, that these parameters are not always correlated with disease progression or response to treatment. Subsequent advances in molecular diagnosis have increasingly allowed establishment of virologic criteria (measurement of plasma HCV RNA) to evaluate efficacy of treatment in patients with chronic HCV infection.

The ALT is an indirect measure of hepatic inflammation and is elevated with any injury to hepatocytes. The ALT has and is still being used to monitor disease activity and response to treatment; however, the degree of elevation of this enzyme in the blood is not necessarily an accurate reflection of the degree of hepatic inflammation or fibrosis.

The role of liver biopsy in the treatment and study of chronic HCV infection is unclear at this time. Liver biopsy has long been considered the gold standard for assessing the degree of hepatic inflammation and fibrosis and is commonly obtained before treatment. The liver damage in chronic HCV hepatitis is thought to be mainly due to host immune responses rather than a direct cytopathic effect of the virus itself. Although the value of liver biopsy may be influenced by sampling bias allowing for over or underestimation of the extent of liver disease, histopathologic analysis of liver tissue allows for the assessment of disease activity, exclusion of other potential causes of liver disease, evaluation of prognostic factors, and provides information to guide future management. Post-treatment biopsies have provided valuable information in a number of clinical trials; in these studies there was a high correlation between antiviral response and improvements in inflammation. Its value as an endpoint in clinical trials, however, has been limited in some studies by substantial amounts of missing data, when patients refuse to return for post treatment biopsies.

Testing for serum levels of HCV by either PCR for RNA or bDNA can provide important information on viral activity. Measurement of HCV RNA has become the preferred means of assessing treatment response than either ALT level or histopathology. Quantitative assessment of HCV RNA during treatment is becoming the strongest predictor of sustained response during interferon or combination therapy for chronic hepatitis C. Furthermore, low serum HCV RNA levels have been correlated with a higher likelihood of response to interferon treatment. However, it remains unknown if a sustained antiviral response will ultimately result in a reduced risk of cirrhosis and/or HCC. Additionally, the relationship between undetectable viral RNA levels and ongoing viral replication is not known.

Prognostic factors that have been reported to be associated with more favorable responses to treatment include HCV infection with genotypes 2 and 3, low serum HCV-RNA levels ($<2 \times 10^6$ copies/mL), and the absence of cirrhosis. Prognostic factors associated with poor responses to treatment include genotype 1 (60-70% of patients) and African American race.

B.2. Natural, consensus and pegylated interferon monotherapy

Interferon alfa-2a and alfa 2b have been used for the treatment of HCV infection since the early 1990's. The recommended dose is three million units administered subcutaneously three times per week for up to 12 months. Sustained virologic and biochemical response rates range between 10-20% six months after cessation of treatment. Consensus interferon is a genetically engineered compound synthesized by combining the most common amino acid sequences from the naturally occurring alfa interferons. Although it has reportedly greater cytokine induction, antiviral, antiproliferative, natural killer cell and gene induction activities *in vitro* than both the alfa interferons, clinical studies showed viral response rates similar to those achieved with interferon-alfa monotherapy.

The combination of polyethylene glycol (PEG) with interferon increases its half-life allowing for once weekly rather than thrice-weekly administration and with increased anti-viral activity. PEG-Intron™ (Peginterferon alfa-2b) was recently approved as a monotherapy for treatment of chronic HCV in interferon naïve patients. Clinical trial data demonstrated a 18%-25% sustained virologic response at six months following cessation of therapy among patients treated for one year with PEG-Intron compared to 12% among those treated with Intron A alone.

B.3. Interferon and Ribavirin Combination Therapy

Ribavirin is a guanosine analogue that has *in vitro* antiviral activity against a number of different RNA viruses including HCV. Oral ribavirin monotherapy has no effect on HCV-RNA levels or liver histology. While normalization of ALT occurred in 40% of patients in some studies, once therapy was discontinued ALT levels returned to pre-treatment levels. The combination of Intron A and ribavirin (Rebetron Combination Therapy™) is approved for the treatment of chronic HCV infection in patients who relapsed following a response to previous interferon monotherapy and in interferon-naïve patients.

In studies supporting the approval of Rebetron™, patients who initially responded to interferon and subsequently relapsed were treated with ribavirin and Intron A for six months followed by a six-month off-treatment period. At the end of this six-month off-treatment period, patients treated with the combination achieved sustained virologic response rates of 45% compared to 4% for patients treated with interferon monotherapy. Fifty percent of patients treated with combination therapy demonstrated histologic improvement compared to 33% of those in the monotherapy arm. In interferon-naïve patients, treatment with the combination of Intron A and ribavirin resulted in a sustained antiviral response rate of 35% compared to 10% among those treated with Intron A alone.

Recently, results of studies of combination therapy with weekly PEG-Intron and daily ribavirin have been reported, suggesting a small additional benefit with the use of PEG-Intron instead of Intron A.

B.4. Safety profile of interferons and Ribavirin

Significant toxicity has been associated with the use of interferon or pegylated interferon, alone or in combination with ribavirin. The most common adverse effects are fatigue, flu-like symptoms (fatigue, fever, headache and myalgia), depression, gastrointestinal symptoms, and myelosuppression. Some of the adverse effects can be life-threatening, particularly psychiatric manifestations. Some patients become seriously depressed and require hospitalization, have suicidal ideation, or attempt or successfully complete suicide. Interferons have also been observed to be associated with serious renal, pulmonary, endocrine, cardiovascular, and rheumatologic adverse effects. In most cases, these adverse events resolve after stopping therapy.

Patients receiving pegylated interferons experience a somewhat higher number of clinically manifested adverse events (e.g., injection site reactions, fever, rigors, nausea) compared to patients receiving non-pegylated interferon. In addition, pegylated interferon is a more potent suppressor of bone marrow function than non-pegylated interferon, sometimes resulting in severe decreases in neutrophil or platelet counts.

The primary dose-limiting toxicity of ribavirin is hemolytic anemia. Most patients will have a reduction in hemoglobin between 1-3 gm/dL within the first four weeks of treatment. The resulting anemia may exacerbate symptoms of coronary disease or result in the deterioration of cardiac function. The anemia is reversible once the dose of ribavirin is reduced or is discontinued. In clinical trials, over 10% of patients required dose modifications for anemia. Ribavirin is also a known teratogen in every animal species tested, is a mutagen, and is embryocidal. In addition, its half-life in red blood cells has been estimated to be 40 days. For these reasons, pregnancy must be avoided during therapy with ribavirin and six months following cessation of therapy.

II. HEPATITIS C IN CHILDREN

A. Epidemiology and Natural History

Little is known about HCV infection in children. Although the Centers for Disease Control estimates that the prevalence of anti-HCV antibodies in children in the United States is 0.2 to 0.4%, the incidence of pediatric hepatitis C infection in the United States is still unknown. In the past, most children were infected with HCV after transfusion with blood or blood products. Adolescents are at risk for the acquisition of HCV because of high-risk behaviors such as intravenous or intranasal drug use, body piercing, or tattooing. Currently, the primary mode of HCV transmission is vertical infection from infected mothers to their infants. The rate of mother-to-child transmission of HCV is 5-6% but increases with detectable or increasing plasma HCV RNA levels, or with HIV coinfection. There is no known method of decreasing the rate of perinatal HCV transmission.

The natural history of HCV infection in children is influenced by the mode of acquisition, the age at the time of acquisition, concomitant infections, ethanol ingestion, viral genotype, and comorbid diseases. In general, infection with HCV during childhood results in an increase in hepatic transaminases with minimal histopathologic changes, fibrosis, cirrhosis, and other serious complications occur years later during adulthood. However, small studies of children with repeated exposure due to multiple transfusions of blood or blood products suggest that these children can develop serious liver disease during childhood. In this population, hemochromatosis may contribute to the development of liver disease. The natural history of HCV infection after mother-to-child transmission is less well understood. Viremia in the neonate may be transient and not associated with liver disease; however, perinatal HCV infection is more commonly associated with biochemical evidence of liver injury during childhood with clinically significant liver disease developing only after 10 to 20 years. Regardless of the mode of acquisition, liver tissue from children with HCV infection usually exhibits only minimal inflammatory changes and rarely shows fibrosis or cirrhosis.

B. Treatment of Chronic HCV Infection in Children

No large, multicenter, randomized, or controlled trials of the treatment of hepatitis C in children have been published. In addition, there is no consensus on the identification of children who might benefit from treatment, when treatment should be initiated, or what treatment regimens should be evaluated. Small studies of the treatment of HCV-infected children with interferon-alfa monotherapy for six to twelve months have demonstrated response rates similar to that seen in adults, with a similar toxicity profile. There are minimal data available evaluating the treatment of children with the combination of interferon-alfa and ribavirin. Very preliminary data suggest that children can achieve sustained virologic responses and tolerate treatment with the combination of interferon-alfa and ribavirin. One concern that has been raised about treating children with ribavirin is because of its potential for mutagenicity and teratogenicity.

C. Drug Development Issues for Children with Chronic HCV Infection

There are a relatively small number of children with chronic HCV infection in the US. Despite this, it is anticipated that children with chronic HCV infection will likely be treated with available therapies even in the absence of labeling for pediatric patients. Labeling of new treatments would likely represent a meaningful therapeutic advance since none are currently approved. Children appear to exhibit a number of characteristics predictive of a good response in adults: younger age, milder inflammation, minimal fibrosis, less frequent cirrhosis, lower levels of viral load, and shorter duration of infection. Since chronic HCV is the leading cause of liver transplantation among adults in the US, it has been postulated that treating in childhood might prevent progression of liver disease later in life.

However, infected children are relatively healthy and often feel well. The currently available therapies cause a number of significant adverse events. There are long-term concerns about interferon since it may slow growth and development and ribavirin because it is a mutagen. A six- to 12-month course of interferon and ribavirin treatment is expensive and yields relatively poor results in adults. Finally, and very importantly, we do not know if a successful response to treatment today will translate into reduced rates of end-stage liver disease or HCC later in life.

III. REGULATORY CONSIDERATIONS IN PEDIATRIC DRUG DEVELOPMENT

The pediatric labeling rule (December, 1994) permitted FDA to label a drug or biological for pediatric use based on extrapolation of adult efficacy data to pediatric patients when the agency "concludes that the course of the disease and the drug's effects are sufficiently similar." Additional data to support pediatric labeling would usually involve pediatric pharmacokinetic data to support pediatric dosing recommendations, and safety studies in the pediatric population.

The aim of the 1994 was to improve pediatric labeling. The rule targeted already marketed drugs and biologicals but imposed no requirement for manufacturers to study new drugs and biologicals in pediatric patients. Rather, sponsors were to determine if there were existing data that would allow the product to be labeled for pediatric use. If data to support pediatric use were not available, labeling was to contain the statement "[T]he safety and efficacy of drug X have not been established in the pediatric population" or, if studies and data were available in some but not all of the pediatric population, the labeling would state the lower age for which the product was indicated.

In 1998, amid growing concern that the 1994 rule did not go far enough to improve labeling for pediatric use, the agency published a rule requiring manufacturers to study drugs and biological products in the pediatric population "if the drug or biological was likely to be used in substantial numbers of pediatric patients or if the product represented a meaningful therapeutic benefit over existing treatments." This rule did not alter the standards by which drugs or biologicals would be studied in pediatric patients; specifically, it continued to allow extrapolation of efficacy findings based on adult studies if applicable.

In addition to FDA regulations, the Food and Drug Modernization Act of 1997 (FDAMA) provided an incentive to sponsors to perform pediatric studies. Submission of study reports that corresponded to a FDA request for information can result in 6 months of marketing exclusivity added to existing patent protection or exclusivity. However, biologics and antibiotics classified as "old": (without existing patent protection or market exclusivity) do not qualify for this incentive.

With respect to the pediatric rule, every sponsor of a new drug or biological product must submit data on pediatric use at the time of submission of a marketing application, or request a deferral or waiver, as appropriate. If studies are deferred, the sponsor and the

agency are to determine a date that the pediatric data are to be submitted to the agency. If the product is studied in adults for a disease or condition that does not occur in pediatric patients, the sponsor may request a waiver from the requirement to conduct pediatric studies.

Table: Differences between the exclusivity provisions of FDAMA and 1998 Rule.

FDAMA	Pediatric Rule
Studies voluntary	Studies required (unless requirement waived)
Studies for the entire moiety	Studies only for the indication sought
Incentive (6 months of exclusivity)	No incentive
Excludes biologicals and old antibiotics	Orphan drugs are exempt

Finally, under the auspices of the International Conference on Harmonization (ICH), representatives of FDA, the U.S. pharmaceutical industry, and their counterparts in Europe and Japan, developed a guidance document for pediatric studies (E11- Clinical Investigation of Medicinal Products in the Pediatric Population). The document addresses issues of timing of pediatric studies (relative to the studies in adults), types of studies, including pharmacokinetic studies, and ethical issues in studying pediatric patients.